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# Selective Synthesis of Secondary Amines via *N*-Alkylation of Primary Amines and Ammonia with Alcohols by Supported Copper Hydroxide Catalysts

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The *N*-alkylation of primary amines and ammonia (in situ generated from urea or aqueous ammonia) with alcohols to secondary amines was efficiently promoted by supported copper hydroxide catalysts, $Cu(OH)_x/Al_2O_3$ and $Cu(OH)_x/TiO_2$. The observed catalysis was truly heterogeneous, and the catalysts could be reused without an appreciable loss of catalytic performance.

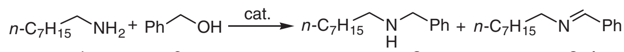
The *N*-alkylation of primary amines to secondary ones is of great importance because the products have been utilized as important synthons for pharmaceuticals, agricultural chemicals, and bioactive compounds.[1] Frequently, alkylhalides have been utilized for the *N*-alkylation with stoichiometric amounts of inorganic bases.[1] However, the reaction with alkylhalides produces large amounts of inorganic salts as wastes.[1]

An alternative environmentally-friendly approach is the *N*-alkylation with alcohols as alkylating reagents in the presence of appropriate transition-metal catalysts, so-called "borrowing hydrogen strategy" (or "hydrogen autotransfer strategy"):[2] The dehydrogenation of an alcohol initially proceeds to afford an aldehyde (more electrophilic than an alcohol), followed by the dehydrative condensation with an amine to produce an imine. Then, the imine is hydrogenated by the transitory formed metal hydride species, giving the desired *N*-alkylated amine. Although many homogeneous catalysts, in particular platinum group metal complexes, have been reported to be active for the *N*-alkylation with alcohols,[2,3] these systems have shortcomings of the recovery and reuse of expensive catalysts and/or the indispensable use of co-catalysts such as bases and stabilizing ligands. The development of easily recoverable and recyclable heterogeneous catalysts can solve the problems of the homogeneous systems and has received a particular research interest.[4,5]

In this paper, we report that easily prepared inexpensive supported copper hydroxides, $Cu(OH)_x/Al_2O_3$ and $Cu(OH)_x/TiO_2$,[6] can act as efficient heterogeneous catalysts for the *N*-alkylation of primary amines and ammonia (in situ generated from urea or aqueous ammonia) with alcohols. Generally, copper-catalyzed *N*-alkylation reactions require high $H_2$ pressures (≥100 atm), high reaction temperatures (≥160 °C), and/or stoichiometric amounts of bases (e.g., $K_2CO_3$) to attain high yields of desired amines.[5] In contrast, the present *N*-alkylation with supported copper hydroxide catalysts efficiently proceeded under relatively mild reaction conditions (1 atm of Ar, 135 °C) without any co-catalysts.[7]

The catalytic activities for the reaction of *n*-octylamine (**1a**) with benzyl alcohol (**2a**) to form *N*-benzyloctylamine (**3a**) were compared (Table 1). Among various catalysts tested, supported copper hydroxide catalysts such as $Cu(OH)_x/Al_2O_3$ and $Cu(OH)_x/TiO_2$ (see Supporting Information[11] for preparation and characterization) showed the highest catalytic activities and selectivities to the secondary amine **3a** (Entries 1 and 2). No formation of **3a** was observed in the absence of the catalysts (Entry 16) or in the presence of $Al_2O_3$ (Entry 15). The catalyst precursor $CuCl_2\cdot 2H_2O$ and commonly utilized copper salts and complexes such as $Cu(NO_3)_2\cdot 3H_2O$, $Cu(CH_3COO)_2\cdot H_2O$, $Cu(PhCOO)_2$, $Cu(CF_3SO_3)_2$, $Cu(acac)_2$, $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$, CuCl, and $[Cu(C{\equiv}CPh)]_n$ were not effective (Entries 6–14). The catalytic activities of supported copper hydroxides were much higher than those of unsupported $Cu(OH)_2$ (Entry 4) and a physical mixture of $Cu(OH)_2$ and $Al_2O_3$ (Entry 5). The reaction hardly proceeded in the presence of the copper chloride species supported on $Al_2O_3$ prepared without the base pretreatment ($CuCl_2/Al_2O_3$, Entry 3, see Supporting Information[11] for preparation). These results suggest that the generation of the highly dispersed "copper hydroxide species" on the surface of supports is very important to achieve the high catalytic activity and selectivity.[7]

**Table 1.** The *N*-alkylation of **1a** with **2a** by various catalysts[a]




**1a** **2a** **3a** **3a'**

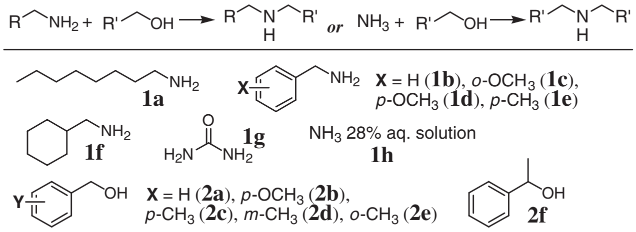
| Entry | Catalyst | Yield/% | |
|---|---|---|---|
| | | **3a** | **3a′** |
| 1 | $Cu(OH)_x/Al_2O_3$ | 85 | 3 |
| 2[b] | $Cu(OH)_x/TiO_2$ | 80 | 4 |
| 3 | $CuCl_2/Al_2O_3$ | nd[f] | 6 |
| 4 | $Cu(OH)_2$ | nd | 10 |
| 5[c] | $Cu(OH)_2 + Al_2O_3$ | nd | 9 |
| 6 | $CuCl_2\cdot 2H_2O$ | nd | 7 |
| 7 | $Cu(NO_3)_2\cdot 3H_2O$ | nd | 9 |
| 8 | $Cu(CH_3COO)_2\cdot H_2O$ | nd | 6 |
| 9 | $Cu(PhCOO)_2$ | nd | 6 |
| 10 | $Cu(CF_3SO_3)_2$ | nd | 7 |
| 11 | $Cu(acac)_2$[d] | nd | 7 |
| 12 | $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$[e] | nd | 8 |
| 13 | CuCl | nd | 6 |
| 14 | $[Cu(C{\equiv}CPh)]_n$ | nd | 8 |
| 15[c] | $Al_2O_3$ | nd | 5 |
| 16 | None | nd | 10 |

[a]Reaction conditions: Catalyst (Cu: 0.04 mmol), **1a** (0.5 mmol), **2a** (2 mmol), mesitylene (2 mL), 135 °C, 65 min, under 1 atm of Ar. Yields (based on **1a**) were determined by GC analyses. [b]60 min. [c]$Al_2O_3$ (200 mg). [d]acac: acetylacetonato. [e]tmen: *N*,*N*,*N′*,*N′*-tetramethylethylenediamine. [f]nd: not detected (<1%).

The $Cu(OH)_x/Al_2O_3$-catalyzed reaction of **1a** with **2a** was carried out under the conditions described in Table 1, and the catalyst was removed from the reaction mixture by hot filtration at ca. 50% yield of **3a**. After removal of the catalyst, the reaction

**Table 2.** The synthesis of various secondary amines[a]




| Entry | N Source | Alcohol | Time/min | Yield/% |
|---|---|---|---|---|
| 1 | **1a** | **2a** | 65 | 85 |
| 2 | **1a** | **2b** | 60 | 84 |
| 3 | **1a** | **2c** | 60 | 81 |
| 4[b] | **1a** | **2c** | 75 | 75 |
| 5 | **1a** | **2f** | 780 | 87 |
| 6 | **1b** | **2c** | 105 | 91 |
| 7 | **1c** | **2a** | 90 | 79 |
| 8 | **1d** | **2a** | 90 | 70 |
| 9 | **1e** | **2a** | 360 | 83 |
| 10 | **1f** | **2a** | 70 | 93 |
| 11 | **1g** | **2a** | 480 | 85 |
| 12[c] | **1g** | **2c** | 480 | 95 |
| 13[c] | **1g** | **2d** | 900 | 91 |
| 14[c] | **1g** | **2e** | 1500 | 98 |
| 15 | **1h** | **2a** | 720 | 80 |

[a]Reaction conditions: Catalyst (Cu: 0.04 mmol), N source (amine: 0.5 mmol, urea: 0.25 mmol, or ammonia: 0.5 mmol), alcohol (2 mmol), mesitylene (2 mL), 135 °C, under 1 atm of Ar. Yields (based on the amounts of nitrogen in N sources) were determined by GC analyses. [b]Reuse experiment. [c]Alcohol (2.5 mmol).

was again carried out with the filtrate under the same conditions, and no further reaction proceeded. In addition, it was confirmed by inductively coupled plasma atomic emission spectroscopy that no copper was detected in the filtrate (below detection limit of 7 ppb). The catalyst retrieved after the *N*-alkylation could be reused without significant loss of catalytic performance (Entry 4 in Table 2).[8] All these results can rule out any contribution to the observed catalysis from copper species that leached into the reaction solution and the observed catalysis is truly heterogeneous.[9]

Next, the scope of the present $Cu(OH)_x/Al_2O_3$-catalyzed *N*-alkylation was examined (Table 2). Various combinations of substrates (eight nitrogen sources and six alcohols) have been investigated, and all reactions efficiently proceeded to afford the corresponding unsymmetrically as well as symmetrically substituted secondary amines in high yields without any co-catalysts such as bases. When urea (**1g**) was used as a nitrogen source, the corresponding symmetrically substituted secondary amines could be obtained in high yields through the *N*-alkylation of in situ generated ammonia from **1g** (Entries 11–14).[4b,10] In addition, aqueous ammonia could be directly utilized for the present *N*-alkylation (Entry 15).

The reaction profiles for the $Cu(OH)_x/Al_2O_3$-catalyzed *N*-alkylation of **1a** with **2a** showed that **3a′** was initially formed, followed by the formation of **3a**. Under aerobic conditions, the reaction of **1a** with **2a** exclusively gave **3a′** without the formation of **3a** (Figure S1).[11] It was confirmed in a separate experiment that the oxidative dehydrogenation of alcohols and the hydrogenation of imines to amines in the presence of alcohols efficiently proceeded with the $Cu(OH)_x/Al_2O_3$ catalyst (Figure S1).[11] Thus, the present *N*-alkylation likely proceeds via the following three sequential reactions. First, the dehydrogenation of an alcohol to a carbonyl compound proceeds with the transitory formation of the copper hydride species. Then, the carbonyl compound readily reacts with a starting amine to form the corresponding imine. Finally, the hydrogen transfer reaction from the hydride species to the imine proceeds to afford the corresponding secondary amine.

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10 It was confirmed by the separate experiments that **1g** was hydrolytically decomposed to ammonia by the presence of $Al_2O_3$ or $TiO_2$ under similar conditions described in Table 2.

11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.


  